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Original Research Article

Colistin-based combination therapy improving *Acinetobacter baumannii* eradication efficacy

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Abstract

***Acinetobacter baumannii* may cause serious infections in critically ill patients. Colistin often remains the only therapeutic option. In this meta-analysis, we aimed to compare the microbiological eradication rate of colistin-based combination therapy with monotherapy in patients with *A. baumannii* infection. We searched PubMed, Google Scholar and The Cochrane Central Register of Controlled Trials. Data analysis was performed by using Review Manager 5.2 and STATA 12.0 software. A total of seven studies were included in the meta-analysis. Our analysis showed that odds ratio (95% confidence interval (CI)) of overall microbiological eradication was 1.62 (1.16 – 2.27). Results remained robust after sensitivity analysis. The available results suggested that the eradication rate of *A. baumannii* was relatively higher in the combination therapy group than the monotherapy group.**

Keywords: Colistin, Polymyxin, *Acinetobacter baumannii*, Meta-analysis

INTRODUCTION

Acinetobacter baumannii is a Gram-negative coccobacillus that has emerged as a cause of infections acquired in hospitals, particularly in intensive care units (ICUs). Resistance to all major classes of antibiotics in A. baumannii has essentially increased worldwide in the past decade (Song et al., 2008). Inappropriate treatment of A. baumannii infection is associated with high mortality (Kim et al., 2012). Therefore, the choice of treatment should be carefully considered.

Due to the limited treatment options, an old drug, colistin, has increasingly been used as salvage therapy in these infections (Garnacho-Montero et al., 2003), despite its relatively low intrinsic efficacy, a suboptimal lung penetration, and the risk for significant renal toxicity (Petrosillo et al., 2008). It was discovered in 1949 and used in the 1950s, subsequently falling out of favor in the 1980s because of its perceived adverse side-effects. However, the emergence of multidrug resistant Gram-negative microorganisms, particularly A. baumannii, has prompted the need to reintroduce the colistin into the pharmaceutical market (Falagas et al., 2005). Several in vitro and animal studies have demonstrated its synergistic activity with other agents, such as rifampicin (Song et al., 2007; Lee et al., 2013), sulbactam (Kempf et al., 2012; Cikman et al., 2013), carbapenems (Zusman et al., 2013), ampicillin (Punpanich et al., 2011; Cikman et al., 2013), vancomycin (Gordon et al., 2010), which has stimulated interest in combination therapy.

In recent years, some studies have suggested that colistin combination therapy may be considered in the treatment of patients with *A. baumannii* infection (Batirel et al., 2014). However, the results of these studies were not consistent and no more robust answer of the colistin-based combination therapy over monotherapy was provided. Thus, we performed a meta-analysis to compare the *A. baumannii* eradication rate between colistin-based combination therapy and monotherapy in patients with A. baumanni infection.

MATERIALS AND METHODS

Search strategy

We searched the electronic databases PubMed, Google Scholar and The Cochrane Central Register of Controlled

Trials up to June 2014. A loose search strategy, using the key words "colistin and *baumannii"* or "polymyxin and *baumannii*", was performed in order to maximize the possibility of identifying all relevant records. We also searched the reference lists of all included papers and relevant reviews. If multiple publications of the same trial were retrieved, only the most detailed article was included. Our searches were not limited by publication date and the language was also not restricted to English. The databases search was conducted independently by two authors (Guoming Su and Jiamin Wang). Disagreements were resolved by consensus.

Selection criteria

The search results were then screened on the basis of the following criteria. (1) *Types of studies:* Studies were eligible for inclusion in the meta-analysis if they were randomized controlled trials, controlled clinical studies, or cohort studies with designs comparing the eradication rate of colistin-based combination therapy with monotherapy for the treatment of *A. baumannii* infection, while review articles, commentaries, letters, observational studies and case series were excluded. (2) *Interventions*: The intervention group was restricted to colistin in combinations with antimicrobial drugs treatment; the control group was colistin monotherapy. Studies of patients receiving aerosolized colistin were excluded. (3) *Outcome*: The microbiological response rate was reported separately for the intervention group and the control group. A microbiological response was considered to be achieved if subsequent cultures were negative for *A. baumannii*. Studies focusing on the susceptibility of clinical isolates to antimicrobials without clinical data were excluded from the meta-analysis.

Data extraction and quality assessment

Two authors (Guoming Su and Jiamin Wang) independently extracted information from eligible studies using a standardized form, and then another author (Zuguo Zhao) verified them. The following information was extracted from each study: first author, year of publication, country, study type, number of patients, clinical characteristics and microbiological outcome.

The Newcastle-Ottawa scale (NOS) (Wells GA, 2012) was used to assess the quality of each study included in the meta-analysis. NOS scores ranged from 0 to 9, in which NOS score < 3 were classified as poor quality and in which NOS score ≥ 3 considered as high quality. Quality assessment was performed by two independent authors and then disagreements were resolved by discussion.

Data analysis

Mantel-Haenszel method was used to calculate odds ratio (OR) and their 95% confidence intervals (CI). We conducted a fixed-effect model meta-analysis for homogeneous outcomes and a random-effects model for heterogeneous outcomes. We quantified the effect of heterogeneity using $I2 = 100\% \times (Q - df) / Q$, where I2 measures the degree of inconsistency between studies and determines whether the percent total variation across studies is due to heterogeneity rather than to chance. I2 ranges between 0% and 100%, and I2 values of 25%, 50% and 75% are referred to as low, moderate and high estimates. If I2 statistic (> 50%) indicated heterogeneity between studies, a random-effects model was calculated. Otherwise, fixed-effects models were calculated. A sensitivity analysis was also conducted by excluding the studies that had a high risk of bias. These analyses were performed using Review Manager (Version 5.2. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2012). We used the Begg's funnel plot (Begg and Mazumdar, 1994) and Egger's linear regression method (Egger et al., 1997) to evaluate the presence of publication bias, which were conducted by STATA 12.0 software (StataCorp, 2011). A p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Search Results

A total of 954 titles and abstracts were found from initial searches of the electronic databases. We applied the eligibility criteria to filter out 922 of these articles based on examination of the title and abstract. An additional 25 articles were further excluded after full text review. Therefore, our final database included 7 studies (Falagas et al., 2010; Simsek et al., 2012; Aydemir et al., 2013; Durante-Mangoni et al., 2013; Garnacho-Montero et al., 2013; Batirel et al., 2014; Kalin et al., 2014) comprising 852 participants in the meta-analysis. The details of study selection flow are described in Figure 1.

Study characteristics

The main characteristics of the studies are shown in Table 1. The publication years of included studies ranged from 2010 to 2014. A total of 576 patients were included in the intervention group and 276 were included in the control group. Colistin was given in combinations with rifampicin (Simsek et al., 2012; Aydemir et al., 2013; Durante-Mangoni et al., 2013), sulbactam (Simsek et al., 2012; Batirel et al., 2014; Kalin et al., 2014), carbapenems (Falagas et al., 2010; Simsek et al., 2012;

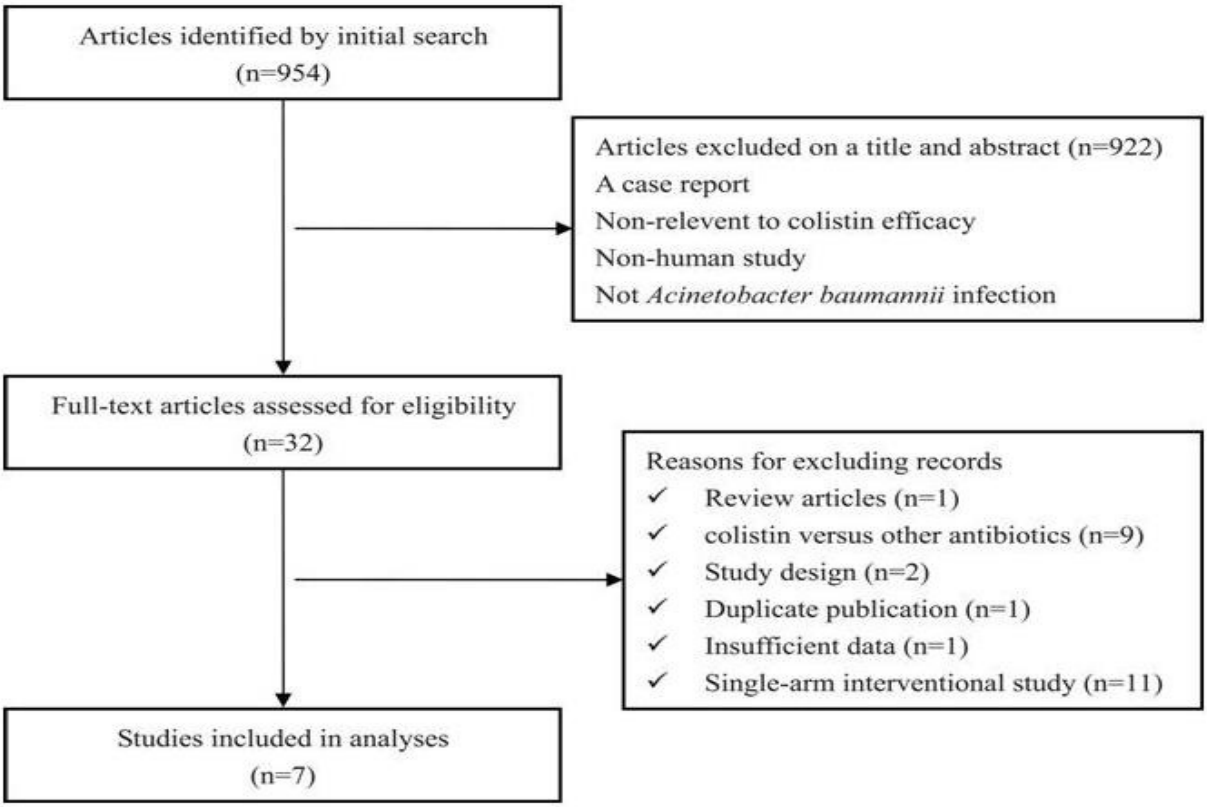

Figure 1. Study flow diagram.

Table 1. Characteristics of studies included in primary analysis.

First author, year	Country	Study design	Site of infection	Resistance status	No. of participants	Age (years)	Drugs given with colistin	Follow-up (days)	NOS score
Durante-Mangoni E, 2013	Italy	RCT	VAP, HAP, BSI, IAI	XDR	209	62 (15.4)	rifampicin	30	8
Kalin G, 2014	Turkey	retrospective	VAP	MDR	82	63 (20–89) 52 (19–96)	sulbactam	14	7
Batirel A, 2014	Turkey	retrospective	BSI	XDR	250	59.1±19.6 58.3±20.5	carbapenem; sulbactam;	14	8
Simsek F, 2012	Turkey	retrospective	VAP, BSI, IAI et al.	COS	51	51.71±18.82	rifampicin; carbapenem; sulbactam et al.	1–132	6
Aydemir H, 2013	Turkey	prospective	VAP	carbapenem-resistance	43	61 ± 20	rifampicin	20	8
Garnacho-Montero J, 2013	Spain	retrospective	VAP, bacteremia	carbapenem-resistance	47	54±14.8 63±11.6	vancomycin	28	7
Falagas ME, 2010	Greece	retrospective	Pneumonia, bacteraemia et al	MDR	170	66.6±14.4 59.6±19.1	meropenem; ampicillin; piperacillin et al.	10–22	6

RCT, randomized controlled trial; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; BSI, bloodstream infection; IAI, intra-abdominal infection; XDR, extensively drug-resistant; MDR, multidrug-resistant; COS, colistin-only-susceptible.

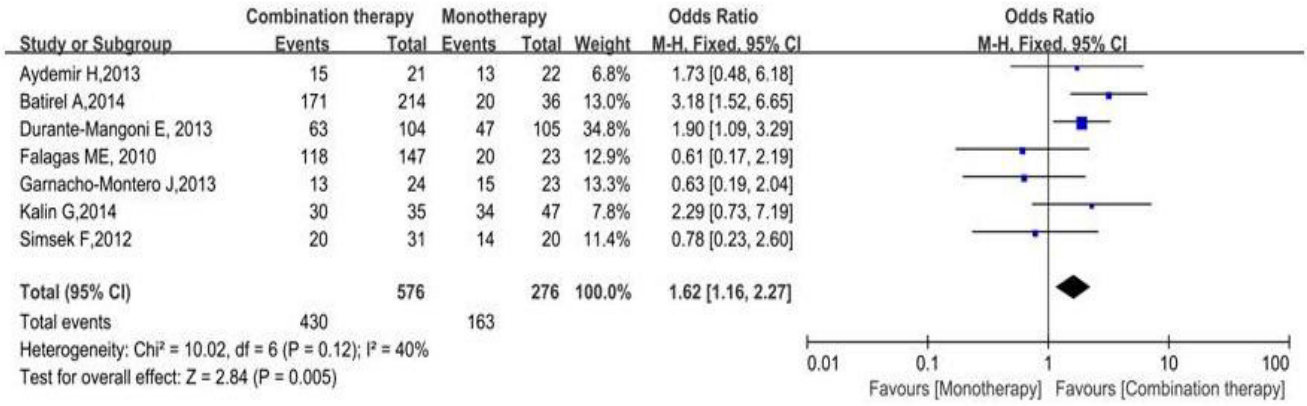

Figure 2. Forest plot of the microbiological eradication rate in *A. baumannii* infection patients.

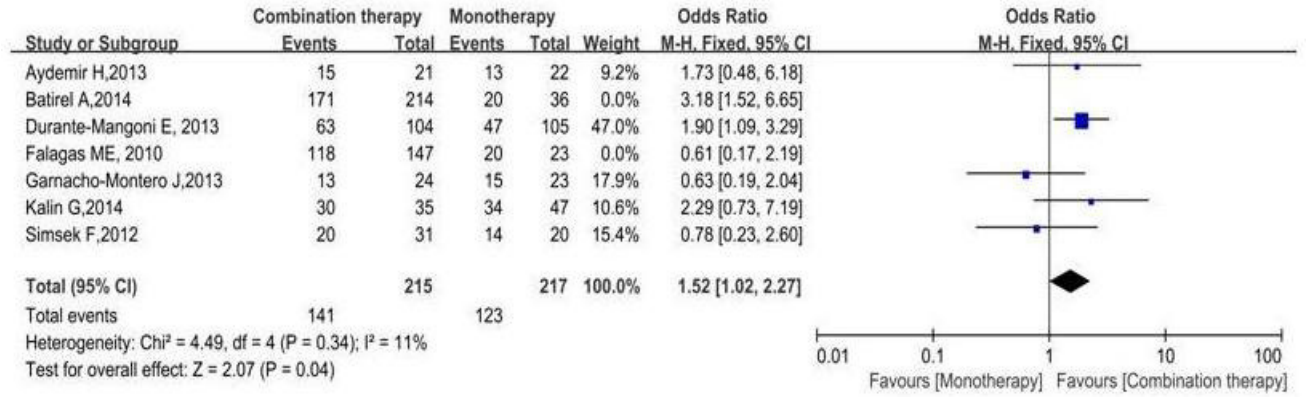

Figure 3. Forest plot of the microbiological eradication rate in *A. baumannii* infection patients after sensitivity analysis.

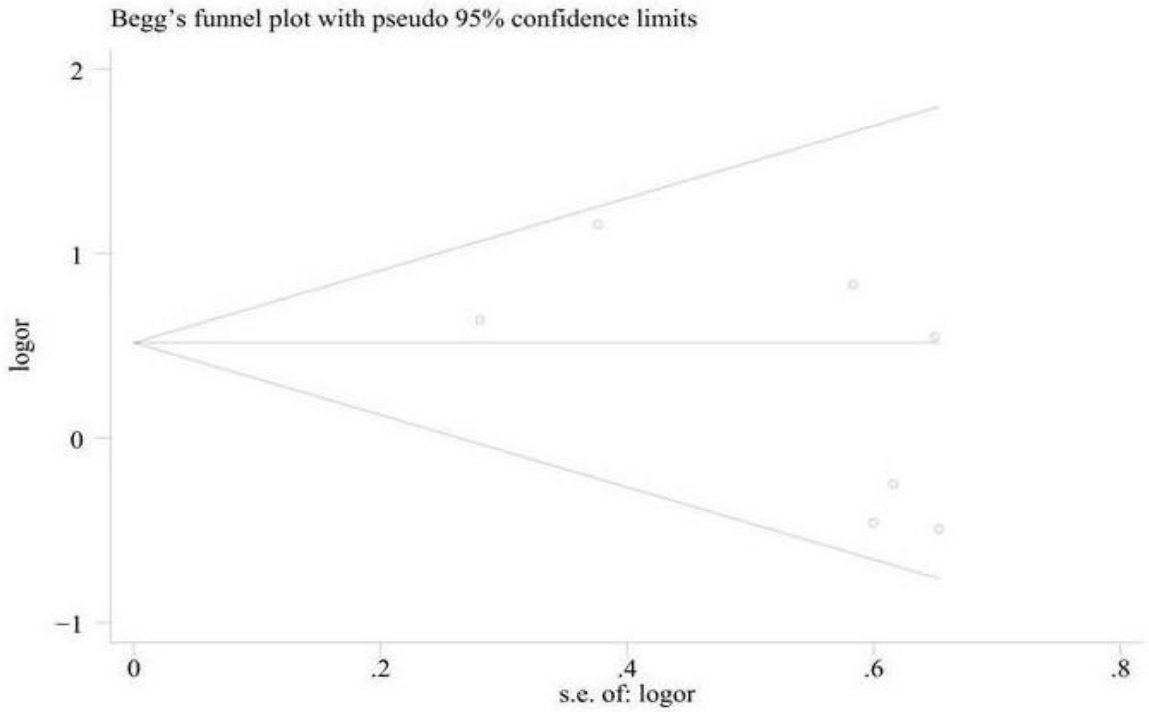

Figure 4. Begg's funnel plot for the assessment of potential publication bias.

Batirel et al., 2014), tigecycline (Simsek et al., 2012), ampicillin (Falagas et al., 2010; Simsek et al., 2012), vancomycin (Garnacho-Montero et al., 2013) or piperacillin (Falagas et al., 2010). The level of evidence for each study was graded from scores 6 to 8 according to the NOS, suggesting that all studies were high quality.

The main result of meta-analysis

As was shown in Figure 2, no significant heterogeneity (I2 = 40%) was observed. Therefore, fixed effects model was used to pool the results. The OR of the overall microbiological eradication for patients treated with colistin-based combination therapy compared with monotherapy was 1.62 (95% CI: 1.16 – 2.27), which was statistically significant (p = 0.005) (Figure 2). The pooling result showed that the microbiological eradication rate of colistin-based combination therapy was relatively higher than monotherapy in *A. baumannii* infection patients.

Sensitivity analysis

Sensitivity analysis was conducted by omitting the two studies by Batirel et al (Batirel et al., 2014) and Falagas et al (Falagas et al., 2010). As was shown in Figure 3, no significant statistical heterogeneity (I2 = 11%) was noted for this outcome. Therefore, fixed effects model was used to pool the results. A significant increase of microbiologic eradication rate was observed in the colistin-based combination therapy (p = 0.04) (Figure 3), indicating that results remained robust after sensitivity analysis.

Publication bias

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures, and there was no evidence of publication bias (Begg's test p = 0.230, Egger's test p = 0.149). In addition, no obvious asymmetry was identified in the funnel plots (Figure 4).

DISCUSSION

We performed a meta-analysis to evaluate the best available research evidence regarding the microbiological eradication rate for colistin-based combination therapy in *A. baumannii* infection patients. Only a small number of studies (Falagas et al., 2010; Simsek et al., 2012; Aydemir et al., 2013; Durante-Mangoni et al., 2013; Garnacho-Montero et al., 2013; Batirel et al., 2014; Kalin et al., 2014), involving a relatively small number of patients, met the eligibility criteria. Although only seven studies were included in the present study, quality assessment suggested that the overall study quality was fair, and no significant publication bias was detected. Analysis of the data extracted from included studies revealed that colistin-based combination therapy was superior to monotherapy for the eradication of *A. baumannii.*

In a retrospective study conducted by Batirel et al (Batirel et al., 2014), a total of 218 patients who received colistin-based combination therapy and only 37 patients who received monotherapy were enrolled in this meta-analysis. And their result of microbiological eradication rate clearly favored colistin-based combination therapy over the monotherapy. Another retrospective study conducted by Falagas et al (Falagas et al., 2010) , in which a total of 147 patients received colistin-based combination therapy but only 23 patients were included in the monotherapy group. Therefore, we guessed that the two studies had a high risk of bias. So we performed a sensitivity analysis by omitting them. However, when the two studies were excluded in the sensitive analysis, heterogeneity is lower than preliminary analysis and the results remained robust.

The main rationale for colistin-based combination therapy lies in the existence of in vitro synergy. Several in vitro studies have demonstrated synergistic activity of colistin combinations with other antimicrobial agents against isolates of *A. baumannii*, such as rifampicin (Wareham and Bean, 2006), carbapenems (Wareham and Bean, 2006; Pankey and Ashcraft, 2009), ampicillin (Cikman et al., 2013). Further, a meta-analysis conducted by Zusman et al (Zusman et al., 2013) implied that the combination of carbapenems with polymyxins against *A. baumannii* was supported in vitro by high synergy rates, with less resistance development. Therefore, colistin-based combination therapy is being recommended against monotherapy due to selection of heteroresistant strains during prolonged colistin therapy (David and Gill, 2008). Based on our meta-analysis, in combination with previous studies, we modestly suggest that critically ill patients with *A. baumannii* infection should be treated with colistin-based combination therapy.

There are several limitations of our meta-analysis. First of all, only a small number of studies met our inclusion criteria, which is likely to produce inaccuracies in outcome reporting. Even though our searches were extensive, we cannot be absolutely sure that all relevant articles were located. Furthermore, this meta-analysis was only based on published data. Although publication bias was not identified in this meta-analysis, the possibility of omission of unpublished or ongoing studies could not be excluded. Additionally, although clear inclusion and exclusion criteria were made, significant differences still existed among study design, resistance status and site of infection.

In conclusion, our meta-analysis suggested that the eradication rate of *A. baumannii* was relatively higher in colistin-based combination therapy group than the monotherapy group. However, further meta-analysis

should be performed in the future involving more known studies with analysis of subgroups by site of infection or resistance status.

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Conflict of interest statement

The authors have declared that no competing interests exist.

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